General

Guideline Title

Identification and management of familial hypercholesterolaemia.

Bibliographic Source(s)

National Collaborating Centre for Primary Care. Identification and management of familial hypercholesterolaemia. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 Aug. 45 p. (Clinical guideline; no. 71).

Guideline Status

This is the current release of the guideline.

The National Clinical Guidelines Centre (formerly the National Collaborating Centre for Primary Care) reaffirmed the currency of this guideline in 2011.

Recommendations

Major Recommendations

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre for Primary Care (NCCPC) on behalf of the National Institute for Health and Clinical Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Diagnosis

See also section 'Information needs and support' below.

Healthcare professionals should consider the possibility of familial hypercholesterolaemia (FH) in adults with raised cholesterol (total cholesterol typically greater than 7.5 mmol/L), especially when there is a personal or a family history of premature coronary heart disease.

Healthcare professionals should exclude secondary causes of hypercholesterolaemia before a diagnosis of FH is considered.

A diagnosis of FH should be made using the Simon Broome criteria, which include a combination of family history, clinical signs (specifically tendon xanthomata), cholesterol concentration and DNA testing (see appendix E in the original guideline document).

Healthcare professionals should inform people with a diagnosis of FH based on the Simon Broome criteria (see appendix E in the original guideline document) that they have a clinical diagnosis of FH.

Healthcare professionals should consider a clinical diagnosis of homozygous FH in adults with a low-density lipoprotein cholesterol (LDL-C)

concentration greater than 13 mmol/L and in children/young people with an LDL-C concentration greater than 11 mmol/L. All people with a clinical diagnosis of homozygous FH should be offered referral to a specialist centre.

To confirm a diagnosis of FH, healthcare professionals should undertake two measurements of LDL-C concentration because biological and analytical variability occurs.

Healthcare professionals should be aware that the absence of clinical signs (for example, tendon xanthomata) in adults and children/young people does not exclude a diagnosis of FH.

A family history of premature coronary heart disease should always be assessed in a person being considered for a diagnosis of FH (see Simon Broome criteria, appendix E in the original guideline document).

When considering a diagnosis of FH, healthcare professionals with expertise in FH should use standardised pedigree terminology to document, when possible, at least a three-generation pedigree. This should include relatives' age of onset of coronary heart disease, lipid concentrations and smoking history. For deceased relatives, the age and cause of death, and smoking history should be documented. If possible, the index individual should verify this information with other family members.

Ultrasonography of the Achilles tendon is not recommended in the diagnosis of FH.

Coronary heart disease risk estimation tools such as those based on the Framingham algorithm should not be used because people with FH are already at a high risk of premature coronary heart disease.

Healthcare professionals should offer people with a clinical diagnosis of FH a DNA test to increase the certainty of their diagnosis and to aid diagnosis among their relatives.

Healthcare professionals should inform all people who have an identified mutation diagnostic of FH that they have an unequivocal diagnosis of FH even if their LDL-C concentration does not meet the diagnostic criteria (see appendix E in the original guideline document).

In a family where a DNA mutation is identified, not all family members may have inherited the mutation. When DNA testing has excluded FH in a member of a family, healthcare professionals should manage the person's coronary heart disease risk as in the general population (see the NICE clinical guideline 67, 'Lipid Modification: cardiovascular risk assessment and modification of blood lipids for the primary and secondary prevention of cardiovascular disease').

In children at risk of FH because of one affected parent, the following diagnostic tests should be carried out by the age of 10 years or at the earliest opportunity thereafter.

- A DNA test if the family mutation is known.
- LDL-C concentration measurement if the family mutation is not known. When excluding a diagnosis of FH a further LDL-C measurement should be repeated after puberty because LDL-C concentrations change during puberty.

In children at risk of homozygous FH because of two affected parents or because of the presence of clinical signs, for example, cutaneous lipid deposits (xanthomata), LDL-C concentration should be measured before the age of 5 years or at the earliest opportunity thereafter. If the LDL-C concentration is greater than 11 mmol/L then a clinical diagnosis of homozygous FH should be considered.

Identifying People with FH Using Cascade Testing

Healthcare professionals should use systematic methods (that is, cascade testing) for the identification of people with FH.

Healthcare professionals should offer all people with FH a referral to a specialist with expertise in FH for confirmation of diagnosis and initiation of cascade testing.

Healthcare professionals with expertise in FH should explain what is meant by cascade testing, and discuss its implications with all people with FH.

Cascade testing using a combination of DNA testing and LDL-C concentration measurement is recommended to identify affected relatives of those index individuals with a clinical diagnosis of FH. This should include at least the first- and second- and, when possible, third-degree biological relatives.

In families in which a mutation has been identified, the mutation and not LDL-C concentration should be used to identify affected relatives. This should include at least the first- and second- and, when possible, third-degree biological relatives.

In the absence of a DNA diagnosis, cascade testing using LDL-C concentration measurements should be undertaken to identify people with FH.

To diagnose FH in relatives of an index individual, the gender- and age-specific criteria for LDL-C concentration in appendix E should be used. The Simon Broome LDL-C criteria for index individuals should not be used because this will result in under diagnosis.

The use of a nationwide, family-based, follow-up system is recommended to enable comprehensive identification of people affected by FH.

Healthcare professionals should be aware of the latest guidance on data protection when undertaking cascade testing.

Management

Drug Treatment

Adults

When offering lipid-modifying drug therapy to adults with FH, healthcare professionals should inform the person that this treatment should be lifelong.

Statins should be the initial treatment for all adults with FH.

Healthcare professionals should consider prescribing a high-intensity statin to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline (that is, LDL-C concentration before treatment).

The dose of statin should be increased to the maximum licensed or tolerated dose to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline (that is, LDL-C concentration before treatment).

Healthcare professionals should offer treatment with a statin with a low acquisition cost for adults with FH in whom the diagnosis is made after the age of 60 and who do not have coronary heart disease.

Ezetimibe monotherapy is recommended as an option for the treatment of adults with heterozygous-familial hypercholesterolaemia who would otherwise be initiated on statin therapy but who are unable to do so because of contraindications to initial statin therapy.*

Ezetimibe monotherapy is recommended as an option for the treatment of adults with heterozygous-familial hypercholesterolaemia who are intolerant to statin therapy (as defined below).*

Ezetimibe, coadministered with initial statin therapy, is recommended as an option for the treatment of adults with heterozygous-familial hypercholesterolaemia who have been initiated on statin therapy when:*

- Serum total or LDL-C concentration is not appropriately controlled (as defined below) either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy (as defined below)
- Consideration is being given to changing from initial statin therapy to an alternative statin.

When the decision has been made to treat with ezetimibe coadministered with a statin, ezetimibe should be prescribed on the basis of lowest acquisition cost.*

For the purposes of this guidance, appropriate control of cholesterol concentrations should be based on individualised risk assessment in accordance with national guidance on the management of cardiovascular disease for the relevant populations.*

For the purposes of this guidance, intolerance to initial statin therapy should be defined as the presence of clinically significant adverse effects from statin therapy that are considered to represent an unacceptable risk to the patient or that may result in compliance with therapy being compromised. Adverse effects include evidence of new-onset muscle pain (often associated with levels of muscle enzymes in the blood indicative of muscle damage), significant gastrointestinal disturbance or alterations of liver function tests.*

* These recommendations are from the National Institute for Health and Clinical Excellence [NICE] technology appraisal guidance 132. See the NICE guideline Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. They have been incorporated into this guideline in line with NICE procedures for developing clinical guidelines.

Prescribing of drug therapy for adults with homozygous FH should be undertaken within a specialist centre.

Healthcare professionals should offer adults with FH a referral to a specialist with expertise in FH if treatment with the maximum tolerated dose of a high-intensity statin and ezetimibe does not achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline (that is, LDL-C concentration before treatment).

Healthcare professionals should offer adults with FH a referral to a specialist with expertise in FH for consideration for further treatment if they are

assessed to be at very high risk of a coronary event, that is, if they have any of the following:

- Established coronary heart disease
- A family history of premature coronary heart disease
- Two or more other cardiovascular risk factors (for example, they are male, they smoke, or they have hypertension or diabetes)

Adults with FH with intolerance or contraindications to statins or ezetimibe should be offered a referral to a specialist with expertise in FH for consideration for treatment with either a bile acid sequestrant (resin), nicotinic acid, or a fibrate to reduce their LDL-C concentration.

The decision to offer treatment with a bile acid sequestrant (resin), nicotinic acid or a fibrate in addition to initial statin therapy should be taken by a specialist with expertise in FH.

Healthcare professionals should exercise caution when adding a fibrate or nicotinic acid to a statin because of the risk of muscle-related side effects (including rhabdomyolysis). Gemfibrozil and statins should not be used together.

Adults with FH who are prescribed nicotinic acid should be offered advice on strategies that reduce flushing. Such advice should include taking low initial doses with meals and/or aspirin 30 minutes before the first daily dose.

Children and Young People

Healthcare professionals should offer all children and young people diagnosed with, or being investigated for, a diagnosis of FH a referral to a specialist with expertise in FH in children and young people. This should be in an appropriate child/young person-focused setting that meets the standards within the 'National service framework for children, young people and maternity services' (available from www.dh.gov.uk).

Lipid-modifying drug therapy for a child or young person with FH should usually be considered by the age of 10 years. The decision to defer or offer lipid-modifying drug therapy for a child or young person should take into account:

- Their age
- The age of onset of coronary heart disease within the family
- The presence of other cardiovascular risk factors, including their LDL-C concentration

When offering lipid-modifying drug therapy for children or young people, healthcare professionals should inform the child/young person and their parent/carer that this treatment should be lifelong.

When the decision to initiate lipid-modifying drug therapy has been made in children and young people, statins should be the initial treatment. Healthcare professionals with expertise in FH in children and young people should choose a statin that is licensed for use in the appropriate age group.

Statin therapy for children and young people with FH should usually be prescribed at the doses specified in the 'British national formulary (BNF) for children.'

In exceptional instances, for example, when there is a family history of coronary heart disease in early adulthood, healthcare professionals with expertise in FH in children and young people should consider offering:

- A higher dose of statin than is licensed for use in the appropriate age group
- More than one lipid-modifying drug therapy
- Lipid-modifying drug therapy before the age of 10 years

In children and young people with homozygous FH, LDL-C concentration may be lowered by lipid-modifying drug therapy and this should be considered before LDL apheresis (see section "Specialist treatment," below).

In children and young people with FH who are intolerant of statins, healthcare professionals should consider offering other lipid-modifying drug therapies capable of reducing LDL-C concentration (such as bile acid sequestrants [resins], fibrates or ezetimibe).

Routine monitoring of growth and pubertal development in children and young people with FH is recommended.

Adults and Children/Young People

Decisions about the choice of treatment should be made following discussion with the adult or child/young person and their parent/carer, and be informed by consideration of concomitant medication, comorbidities, safety and tolerability.

Healthcare professionals should consider offering fat-soluble vitamin (vitamins A, D and K) and folic acid supplementation for adults or children/young people with FH who are receiving long-term treatment with bile acid sequestrants (resins).

Healthcare professionals should offer people with FH a referral to a specialist with expertise in FH if they are experiencing side effects that compromise concordance with lipid-modifying drug therapy.

When the decision has been made to offer adults or children/young people with FH treatment with a statin, baseline liver and muscle enzymes (including transaminases and creatine kinase, respectively) should be measured before initiation of therapy. However, people with raised liver or muscle enzymes should not routinely be excluded from statin therapy.

Routine monitoring of creatine kinase is not recommended in asymptomatic adults or children/young people with FH who are receiving treatment with a statin.

Lifestyle Interventions

Healthcare professionals should regard lifestyle advice as a component of medical management, and not as a substitute for lipid-modifying drug therapy.

Diet

All people with FH should be offered individualised nutritional advice from a healthcare professional with specific expertise in nutrition.

People with FH should be advised to consume a diet in which:

- Total fat intake is 30% or less of total energy intake
- Saturated fats are 10% or less of total energy intake
- Intake of dietary cholesterol is less than 300 mg/day
- Saturated fats are replaced by increasing the intake of monounsaturated and polyunsaturated fats

It may be helpful to suggest they look at www.eatwell.gov.uk/healthydiet for further practical advice.

Healthcare professionals should advise people with FH to eat at least five portions of fruit and vegetables a day, in line with national guidance for the general population. Examples of what constitutes a portion can be found at www.eatwell.gov.uk/healthydiet and www.5aday.nhs.uk.

Healthcare professionals should advise people with FH to consume at least two portions of fish a week (one of which should be oily fish). Pregnant women with FH should be advised to limit their oily fish to two portions a week. Further information and advice on healthy cooking methods can be found at www.eatwell.gov.uk/healthydiet.

Healthcare professionals should advise people with FH that if they wish to consume food products containing stanols and sterols these need to be taken consistently to be effective.

People with FH should not routinely be recommended to take omega-3 fatty acid supplements. For people with FH who have already had a myocardial infarction (MI), refer to 'MI: secondary prevention' (see the NICE clinical guideline 48, Post myocardial infarction: secondary prevention in primary and secondary care for patients following a myocardial infarction).

Physical Activity

Healthcare professionals should advise people with FH to take at least 30 minutes of physical activity a day, of at least moderate intensity, at least 5 days a week, in line with national guidance for the general population.*

Healthcare professionals should encourage people with FH who are unable to perform moderate-intensity physical activity at least 5 days a week because of comorbidity, disability, medical conditions or personal circumstances to exercise at their maximum safe capacity.

Recommended types of physical activity include those that can be incorporated into everyday life, such as brisk walking, using stairs and cycling.*

Healthcare professionals should advise people with FH that bouts of physical activity of 10 minutes or more accumulated throughout the day are as effective as longer sessions.*

* See 'At least five a week: evidence on the impact of physical activity and its relationship to health. A report from the Chief Medical Officer' (2004), available from www.dh.gov.uk.

Weight Management

Healthcare professionals should offer people with FH who are overweight or obese appropriate advice and support to achieve and maintain a healthy weight in line with NICE guidance on obesity (see the NICE clinical guideline 43, 'Obesity: guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children').

Alcohol Consumption

As for the general population, alcohol consumption for adult men with FH should be limited to up to 3-4 units a day, and for adult women with FH up to 2-3 units of alcohol a day. Binge drinking should be avoided. Further information can be found at www.eatwell.gov.uk/healthydiet .

Smoking Advice

People with FH, especially children, who do not smoke should be strongly discouraged from starting because of their already greatly increased risk of coronary heart disease.

People with FH who smoke should be advised that, because of their already greatly increased risk of coronary heart disease, they should stop.

Healthcare professionals should offer people who want to stop smoking support and advice, and referral to an intensive support service, in line with the NICE guidance on smoking cessation.

People with FH who are unwilling or unable to accept a referral to an intensive support service should be offered pharmacotherapy in line with NICE guidance on nicotine replacement therapy and bupropion ('Guidance on the use of nicotine replacement therapy [NRT] and bupropion for smoking cessation' [NICE technology appraisal guidance 39]), and varenicline (see the NICE technology appraisal guidance 123, Varenicline for smoking cessation .)

Specialist Treatment

LDL-Lowering Apheresis

Healthcare professionals should consider offering LDL apheresis for the treatment of adults and children/young people with homozygous FH (see "Diagnosis" section, above). The timing of initiation of LDL apheresis should depend on factors such as the person's response to lipid-modifying drug therapy and presence of coronary heart disease.

In exceptional instances (such as when there is progressive, symptomatic coronary heart disease, despite maximal tolerated lipid-modifying drug therapy and optimal medical and surgical therapy), healthcare professionals should consider offering LDL apheresis for the treatment of people with heterozygous FH. This should take place in a specialist centre on a case-by-case basis and data recorded in an appropriate registry.

Healthcare professionals should recommend arteriovenous fistulae as the preferred method of access for people with FH who are offered treatment with LDL apheresis. People should be counselled about possible benefits and complications of this procedure.

Routine monitoring of the person's iron status should be carried out and iron supplementation initiated as required for people with FH who are receiving treatment with LDL apheresis.

Angiotensin-converting enzyme (ACE) inhibitors should not be used in people with FH who are being treated with LDL apheresis. Instead, ACE inhibitors should be substituted with angiotensin-receptor blocking agents.

People with FH who are receiving blood pressure-lowering drug therapy should have this reviewed and considered for discontinuation on the morning of the day of LDL apheresis.

People with FH who are taking warfarin should have this discontinued approximately 4 days before LDL apheresis and substituted with low molecular weight heparin.

People with FH who are receiving anti-platelet therapy should have this continued if they are receiving treatment with LDL apheresis.

Liver Transplantation

Healthcare professionals should consider offering liver transplantation as an option for the treatment of people with homozygous FH after treatment with lipid-modifying drug therapy and LDL apheresis.

The decision to refer for liver transplantation should take place in partnership with the patient and/or their relatives in an appropriate specialist

setting, following a discussion of the benefits and potential harms of undertaking or declining transplantation.

Information Needs and Support

General Information and Support

During the assessment and communication of familial risk, people should receive clear and appropriate educational information about FH, the process of family testing, DNA testing and the measurement of LDL-C concentration.

A healthcare professional with expertise in FH should provide information to people with FH on their specific level of risk of coronary heart disease, its implications for them and their families, lifestyle advice and treatment options.

Healthcare professionals with expertise in FH should encourage people with FH to contact their relatives to inform them of their potential risk and so that cascade testing can take place.

When considering cascade testing, a healthcare professional with expertise in FH should offer to facilitate the sharing of information about FH with family members.

Healthcare professionals should offer people with FH and their families written advice and information about patient support groups.

Information and Counselling on Contraception for Women and Girls with FH

When lipid-modifying drug therapy is first considered for women and girls, the risks for future pregnancy and the fetus while taking lipid-modifying drug therapy should be discussed. This discussion should be revisited at least annually.

Healthcare professionals should give women and girls with FH specific information tailored to their needs and should offer a choice of effective contraceptive methods.

Combined oral contraceptives (COCs) are not generally contraindicated for women and girls being treated with lipid-modifying drug therapy. However, because there is a potential small increased risk of cardiovascular events with the use of COCs, healthcare professionals should consider other forms of contraception. Prescribers should refer to the summary of product characteristics of COCs and the relevant lipid-modifying drugs for their specific contraindications.

Information for Pregnant Women with FH

Healthcare professionals should be aware that, in general, there is no reason to advise against pregnancy or breastfeeding in women with FH.

Healthcare professionals should advise women with FH that lipid-modifying drug therapy should not be taken if they are planning to conceive or during pregnancy, because of the potential risk of fetal abnormality. Women should be advised that lipid-modifying drug therapy should be stopped 3 months before they attempt to conceive.

Women with FH who conceive while taking statins or other systemically absorbed lipid-modifying drug therapy should be advised to stop treatment immediately and they should be offered an urgent referral (see appendix D) to an obstetrician for a fetal assessment. Women should be fully informed about the nature and purpose of the assessment.

Women with FH who have conceived while taking statins or other systemically absorbed lipid-modifying drug therapy and have had a fetal assessment should be given time, opportunity and full information to consider their options (including the advantages and disadvantages) of continuing with their pregnancy.

Shared-care arrangements, to include expertise in cardiology and obstetrics, should be made for women with FH who are considering pregnancy or are pregnant. Such care should include an assessment of coronary heart disease risk, particularly to exclude aortic stenosis. This is essential for women with homozygous FH.

Serum cholesterol concentrations should not be measured routinely during pregnancy.

Women with FH who are pregnant should be advised on the potential risks and benefits of re-starting lipid-modifying drug therapy for the mother and breastfed infant. Resins are the only lipid-modifying drug therapy that should be considered during lactation.

Ongoing Assessment and Monitoring

Review

All people with FH should be offered a regular structured review that is carried out at least annually.

A baseline electrocardiogram (ECG) should be considered for adults with FH.

Healthcare professionals should record the progress of cascade testing among the relatives of a person with FH as part of the structured review. This should include at least the first- and second- and, when possible, third-degree biological relatives. If there are still relatives who have not been tested, further action should be discussed.

Healthcare professionals should update the family pedigree of a person with FH and note any changes in the coronary heart disease status of their relatives as part of the structured review.

This should include at least the first- and second- and, when possible, third-degree biological relatives.

Structured review should include assessment of any symptoms of coronary heart disease and smoking status, a fasting lipid profile, and discussion about concordance with medication, possible side effects of treatment the patient may be experiencing, and any changes in lifestyle or lipid-modifying drug therapy that may be required to achieve the recommended LDL-C concentration.

Referral for Evaluation for Coronary Heart Disease

Healthcare professionals should offer people with FH an urgent referral (see appendix D in the original guideline document) to a specialist with expertise in cardiology for evaluation if they have symptoms or signs of possible coronary heart disease which are not immediately life-threatening. A low threshold for referral is recommended.

A person with FH with symptoms or signs of possible coronary heart disease which are immediately life-threatening (for example, acute coronary syndrome) should be referred to hospital as an emergency in line with advice for the general population.

Healthcare professionals should consider offering people with FH a referral for evaluation of coronary heart disease if they have a family history of coronary heart disease in early adulthood, or two or more other cardiovascular risk factors (for example, they are male, they smoke, or they have hypertension or diabetes).

Upon diagnosis, healthcare professionals should offer all adults and children/young people with homozygous FH a referral for an evaluation of coronary heart disease.

In asymptomatic children and young people with heterozygous FH, evaluation of coronary heart disease is unlikely to detect clinically significant disease and referral should not be routinely offered.

Clinical Algorithm(s)

Clinical algorithms are provided in the original guideline document for:

- Familial hypercholesterolaemia (FH) diagnosis
- FH management

Scope

Disease/Condition(s)

Familial hypercholesterolaemia (FH): heterozygous and homozygous

Note: Most people with FH have inherited a defective gene for FH from only one parent and are therefore heterozygous. Rarely, a person will inherit a genetic defect from both parents and will have homozygous FH or compound heterozygous FH, which will be collectively termed homozygous FH for the purpose of this guideline.

Guideline Category

Counseling

Diagnosis

Evaluation

Management

Prevention

Risk Assessment

Treatment

Clinical Specialty

Cardiology

Endocrinology

Family Practice

Internal Medicine

Medical Genetics

Nutrition

Obstetrics and Gynecology

Pediatrics

Preventive Medicine

Intended Users

Advanced Practice Nurses

Dietitians

Health Care Providers

Patients

Physician Assistants

Physicians

Guideline Objective(s)

To offers best practice advice on the identification and care of people with familial hypocholesterolaemia

Target Population

Adults and children with possible or definite heterozygous or homozygous familial hypocholesterolaemia in the National Health Service (NHS) in England and Wales

Note: Groups not covered include:

- People with secondary hyperlipidaemia
- People with polygenic and combined hyperlipidaemia

People with hypertriglyceridaemia and type III hyperlipoproteinaemia
Children with other abnormalities of lipid metabolism, such as sitosterolaemia or phytosterolemia

Interventions and Practices Considered

Assessment/Diagnosis

1. Family history
2. Assessment of signs and symptoms (Simon Broome criteria)
3. DNA testing
4. Cascade testing

Management/Treatment

Adults

1. Statins
2. Ezetimibe
3. Statin plus ezetimibe combination therapy

Children and Young People

1. Referral to specialist
2. Statins
3. Bile acid sequestrants, fibrates or ezetimibe
4. Routine monitoring of growth and pubertal development

Adults andÂ Children/Young People

1. Fat soluble vitamin (A, D, K) plus folic acid supplementation (if long term use of bile sequestrants)
2. Lifestyle interventions
3. Diet modification
4. Exercise
5. Weight management
6. Limit alcohol consumption
7. Smoking avoidance/cessation
8. Specialist treatment
    - Low density lipoprotein (LDL) lowering apheresis
    - Liver transplantation
9. Provision of information, counseling and support
    - Contraception (for women and girls)
    - Pregnant women

Major Outcomes Considered

- Prevalence of heterozygous and homozygous familial hypocholesterolaemia (FH)
- Prevalence of coronary heart disease in people with FH
- Low density lipoprotein cholesterol (LDL-C) concentration

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre for Primary Care (NCCPC) on behalf of the National Institute for Health and Clinical Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Methods

Literature Search Strategy

The information scientist developed search strategies for each question, with guidance from the Guideline Development Group (GDG), using relevant MeSH (medical subject headings) or indexing terms, and free text terms. Searches were conducted between October 2006 and September 2007. Update searches for all questions were carried out in December 2007 to identify any recently published evidence. Full details of the sources and databases searched and the strategies are available in Appendix B in the original guideline document. In addition to the update searches, we also considered any important evidence published before the final guideline was submitted.

An initial scoping search for published guidelines, systematic reviews, economic evaluations and ongoing research was carried out on the following databases or websites: National Library for Health (NLH) Guidelines Finder, National Guidelines Clearinghouse, Scottish Intercollegiate Guidelines Network (SIGN), Guidelines International Network (GIN), Canadian Medical Association (CMA) Infobase (Canadian guidelines), National Health and Medical Research Council (NHMRC) Clinical Practice Guidelines (Australian Guidelines), New Zealand Guidelines Group, BMJ Clinical Evidence, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and Heath Technology Assessment Database (HTA), NHS Economic Evaluations Database (NHSEED) National Research Register and Current Controlled Trials.

For each clinical question the following bibliographic databases were searched from their inception to the latest date available: Database of Systematic Reviews (CDSR) Database of Abstracts of Reviews of Effects (DARE) Health Technology Database (HTA), MEDLINE, MEDLINE in Process, EMBASE, CINAHL, CENTRAL (Cochrane Controlled Trials Register), Science Citation Index. When appropriate to the question PsycINFO was also searched.

The search strategies were developed in MEDLINE and then adapted for searching in other bibliographic databases. For the pharmacological questions, methodological search filters designed to limit searches to systematic reviews or randomised controlled trials were used. These were developed by the Centre of Reviews and Dissemination and The Cochrane Collaboration. For all other questions, no restriction was placed on study design.

The economic literature was identified by conducting searches in NHS Economic Evaluations Database (NHSEED) and in MEDLINE, MEDLINE in process, EMBASE Science Citation Index, and Social Science Citation Index using an economics search strategy developed by ScHARR at the University of Sheffield.

Databases of the results of the searches for each question or topic area were created using the bibliographic management software Reference Manager.

Identifying the Evidence

After the search of titles and abstracts was undertaken, full papers were obtained if they appeared to address the Key Clinical Questions (KCQs). The highest level of evidence was sought. However observational studies, surveys and expert formal consensus results were used when randomised control trials were not available. In general, only English language papers were reviewed however, for the questions on apheresis the guideline developers also searched for foreign language papers (specifically in Japanese and German) on the advice of the GDG. Following a critical review of the full text paper, articles not relevant to the subject in question were excluded. Studies that did not report on relevant outcomes were also excluded.

The guideline developers also contacted the relevant manufacturers of key drugs for data on the safety of lipid-modifying drugs in children due to the lack of published evidence. This request was conducted according to the process outlined in 'The guidelines manual'. April 2006. London: National Institute for Health and Clinical Excellence. Available from: www.nice.org.uk/guidelinesmanual .

The reasons for rejecting any paper ordered were recorded and details can be seen in Appendix C of the original guideline document.

Health Economics Evidence Review

Identified titles and abstracts from the economic searches were reviewed by a single health economist and full papers obtained as appropriate. No criteria for study design were imposed a priori. In this way the searches were not constrained to randomised controlled trials (RCTs) containing formal economic evaluations.

Papers were included if they were full/partial economic evaluations, considered patients with familial hypercholesterolaemia (FH), were written in English, and reported health economic information that could be generalised to the United Kingdom.

The full papers were critically appraised by the health economist using a standard validated checklist. A general descriptive overview of the studies, their quality, and conclusions was presented and summarised in the form of a narrative review (see also Appendix D of the original guideline document for the full extractions and reasons for exclusion).

Each study was categorized as one of the following: cost effectiveness analysis or cost utility analysis (i.e., cost effectiveness analysis with effectiveness measured in terms of quality adjusted life years [QALYs] or life year gained). Some studies were categorized as 'cost consequences analyses' or 'cost minimisation analyses'. These studies did not provide an overall measure of health gain or attempt to synthesise costs and benefits together. Such studies were considered as partial economic evaluations.

Currency Review

The National Clinical Guidelines Centre (formerly the National Collaborating Centre for Primary Care) undertook a review of this guideline in 2011 and determined that the information is current. See the NICE Web site for the review decision.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Levels of Evidence

Level of Evidence	Type of Evidence
1++	High-quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1â€“	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2+	Well-conducted caseâ€“control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2â€“	Caseâ€“control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytical studies (for example, case reports, case series)

Level of Evidence	4 Type of Evidence Expert opinion, formal consensus

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre forÂ PrimaryÂ CareÂ (NCCPC) on behalf of the National Institute for Health and Clinical Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Critical Appraisal of the Evidence

From the papers retrieved, the Health Service Research Fellow synthesised the evidence for each question or questions into a narrative summary. These form the basis of this guideline. Each study was critically appraised using the Institute's criteria for quality assessment and the information extracted for included studies is given in Appendix CÂ of the original guideline document. Background papers, for example those used to set the clinical scene in the narrative summaries, were referenced but not extracted.

Choice of Outcomes

Familial hypercholesterolaemia (FH) is a condition characterised by abnormally high concentrations of low-density lipoprotein cholesterolÂ (LDL-C). Therefore the Guideline Development Group (GDG) decided that only those papers reporting LDL-C as a primary outcome would therefore be included. This is also reflected in the wording of the recommendations, for example, referral specifically to the measurement of LDL-C concentration, rather than total cholesterol. Initial preference was given to interventions with evidence on clinical outcomes whether in the FH population or similar at-risk populations (persons with a myocardial infarction) where evidence in the FH population was lacking.

Methods Used to Formulate the Recommendations

Expert Consensus

Informal Consensus

Description of Methods Used to Formulate the Recommendations

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre forÂ PrimaryÂ CareÂ (NCCPC) on behalf of the National Institute for Health and Clinical Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Developing Key Clinical Questions (KCQs)

The first step in the development of the guideline was to refine the guideline scope into a series of KCQs. These KCQs formed the starting point for the subsequent review and as a guide to facilitate the development of recommendations by the Guideline Development Group (GDG).

The KCQs were developed by the GDG and with assistance from the methodology team. The KCQs were refined into specific evidence-based questions (EBQs) specifying interventions to search and outcomes to be searched for by the methodology team and these EBQs formed the basis of the literature searching, appraisal and synthesis.

The total list of KCQs identified is listed in Appendix B in the original guideline document. The development team, in liaison with the GDG, identified those KCQs where a full literature search and critical appraisal were essential. Also, where appropriate, high quality evidence in populations other than that of individual with FH was used to corroborate the limited direct evidence. Literature searches were not undertaken where there was already national guidance on the topic to which the guideline could cross refer. This is detailed in Appendix B in the original guideline document.

Forming Recommendations

In preparation for each meeting, the narrative and extractions for the questions being discussed were made available to the GDG one week before the scheduled GDG meeting. These documents were available on a closed intranet site and sent by post to those members who requested it.

GDG members were expected to have read the narratives and extractions before attending each meeting. The GDG discussed the evidence at the meeting and agreed evidence statements and recommendations. Any changes were made to the electronic version of the text on a laptop and projected onto a screen until the GDG were satisfied with these.

All work from the meetings was posted on the closed intranet site following the meeting as a matter of record and for referral by the GDG members.

Areas without Evidence and Consensus Methodology

The table of clinical questions in Appendix BÂ of the original guideline document indicates which questions were searched.

In cases where evidence was sparse, the GDG derived the recommendations via informal consensus methods, using extrapolated evidence where appropriate. All details of how the recommendations were derived can be seen in the 'Evidence to recommendations' section of each of the chapters.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Economic Analysis

The essence of economic evaluation is that it provides a balance sheet of the benefits and harms as well as the costs of each option. A well conducted economic evaluation will help to identify, measure, value and compare costs and consequences of alternative policy options. Thus the starting point of an economic appraisal is to ensure that healthcare interventions are clinically effective and then also cost effective. Although National Institute for Clinical Excellence does not have a threshold for cost effectiveness, interventions with a cost per quality adjusted life year of up to 20,000 poundsÂ are deemed cost effective, those between 20-30,000 poundsÂ may be cost effective and those above 30,000 poundsÂ are unlikely to be judged cost effective. If a particular treatment strategy were found to yield little health gain relative to the resources used, then it could be advantageous to re-deploy resources to other activities that yield greater health gain.

To assess the cost effectiveness of different management strategies in familial hypercholesterolaemia (FH) a comprehensive systematic review of the economic literature relating to FH patients was conducted. For selected components of the guideline original cost effectiveness analyses were performed. The primary criteria applied for an intervention to be considered cost effective were either:

- The intervention dominated other relevant strategies (that is it is both less costly in terms of resource use and more clinically effective compared with the other relevant alternative strategies)
- The intervention cost less than 20,000 poundsÂ per quality-adjusted life-year (QALY) gained compared with the next best strategy (or usual care).

Cost-Effectiveness Modeling

Some areas were selected for further economic analysis if there was likelihood that the recommendation made would substantially change clinical practice in the National Health Service (NHS) and have important consequences for resource use.

The following areas were chosen for further analysis:

1. The use of high intensity statins compared with low intensity statins in the treatment of FH. This was identified as a priority for further evaluation because statins are recommended as the initial treatment for people with FH due to their effects in reducing morbidity and mortality.
2. A cost effectiveness analysis of cascade testing for FH using DNA testing and LDL-C measurements. This was selected as a priority for further evaluation because this approach was recommended for the identification of people with FH and the resource differentials between the alternative approaches were considerable as was the potential eligible population.

Full reports for each analysis are in the Appendix E in the original guideline document. The GDG was consulted during the construction and interpretation of each model to ensure that appropriate assumptions, model structure and data sources were used. All models were done in accordance to the National Institute for Clinical Excellence (NICE) reference case outlined in the 'The guidelines manual'. April 2006. London: National Institute for Health and Clinical Excellence. Available from: www.nice.org.uk/guidelinesmanual .

See the original guideline document for detailed cost-effectiveness and health economic analysis. A costing report and costing template for implementing guidance on identification and management of familial hypercholesterolaemia (refer to "Availability of Companion Documents" field) are also provided.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The guideline was validated through two consultations.

1. The first draft of the guideline (The full guideline, National Institute for Clinical Excellence [NICE] guideline and Quick Reference Guide) were consulted with Stakeholders and comments were considered by the Guideline Development Group (GDG).
2. The final consultation draft of the full guideline, the NICE guideline and the Information for the Public were submitted to stakeholders for final comments.

The final draft was submitted to the Guideline Review Panel for review prior to publication.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is not identified and graded for each recommendation.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Early detection and treatment of familial hypercholesterolaemia to decrease morbidity and mortality
Practice and delivery of patient-centred care that takes into account patients' needs and preferences and gives them the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals

Potential Harms

Adverse events associated with statins include headache, altered liver function, paraesthesia and gastrointestinal effects (including abdominal pain, flatulence, diarrhoea, nausea and vomiting). Rash and hypersensitivity reactions have been reported but are rare. Muscle effects (myalgia, myositis and myopathy) have also been reported with the use of statins. Severe muscle damage (rhabdomyolysis) is a very rare but significant side effect. Further adverse events are associated with individual statins.
Healthcare professionals should exercise caution when adding a fibrate or nicotinic acid to a statin because of the risk of muscle-related side effects (including rhabdomyolysis).Â Gemfibrozil and statins should not be used together.
The palatability and side effects of bile acid sequestrants reduces compliance with therapy.
The combination of statin with fibrates has specific safety issues which have been highlighted in the recommendations.

Contraindications

Contraindications

Combined oral contraceptives (COCs) are not generally contraindicated for women and girls being treated with lipid-modifying drug therapy. However, because there is a potential small increased risk of cardiovascular events with the use of COCs, healthcare professionals should consider other forms of contraception. Prescribers should refer to the summary of product characteristics of COCs and the relevant lipid-modifying drugs for their specific contraindications.

Qualifying Statements

Qualifying Statements

This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer and informed by the summary of product characteristics of any drugs they are considering.

Areas Outside the Remit of the Guideline

- Techniques for liver transplantation
- Measurement and reporting of blood lipids (this is covered by the National Institute for Health and Clinical Excellence [NICE] clinical guideline on cardiovascular risk assessment)
- Population-based screening programmes for familial hypercholesterolaemia (FH)

Implementation of the Guideline

Description of Implementation Strategy

Implementation

The Healthcare Commission assesses the performance of National Health Service (NHS) organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' (available from www.dh.gov.uk). Implementation of clinical guidelines forms part of the developmental standard D2. Core standard C5 says that national agreed guidance should be taken into account when NHS organisations are planning and delivering care.

NICE has developed tools to help organisations implement this guidance (listed below). These are available on the NICE website (http://guidance.nice.org.uk/CG71 ; see also the "Availability of Companion Documents" field).

- Slides highlighting key messages for local discussion
- Costing tools:
  - Costing report to estimate the national savings and costs associated with implementation
  - Costing template to estimate the local costs and savings involved
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally
- Audit support for monitoring local practice

Key Priorities for Implementation

Diagnosis

- A family history of premature coronary heart disease should always be assessed in a person being considered for a diagnosis of familial hypocholesterolaemia (FH) (see Simon Broome criteria, appendix E in the original guideline document).

- In children at risk of FH because of one affected parent, the following diagnostic tests should be carried out by the age of 10 years or at the earliest opportunity thereafter:
  - A DNA test if the family mutation is known
  - Low-density lipoprotein-C (LDL-C) concentration measurement if the family mutation is not known. When excluding a diagnosis of FH a further LDL-C measurement should be repeated after puberty because LDL-C concentrations change during puberty.
- Coronary heart disease risk estimation tools such as those based on the Framingham algorithm should not be used because people with FH are already at a high risk of premature coronary heart disease.

Identifying People with FH Using Cascade Testing

- Healthcare professionals should offer all people with FH a referral to a specialist with expertise in FH for confirmation of diagnosis and initiation of cascade testing (see appendix D in the original guideline document).
- Cascade testing using a combination of DNA testing and LDL-C concentration measurement is recommended to identify affected relatives of those index individuals with a clinical diagnosis of FH. This should include at least the first- and second- and, when possible, third-degree biological relatives.
- The use of a nationwide, family-based, follow-up system is recommended to enable comprehensive identification of people affected by FH.

Management

Adults

- Healthcare professionals should consider prescribing a high-intensity statin to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline (that is, LDL-C concentration before treatment).

Children and Young People

- Healthcare professionals should offer all children and young people diagnosed with, or being investigated for, a diagnosis of FH a referral to a specialist with expertise in FH in children and young people. This should be in an appropriate child/young person-focused setting that meets the standards within the 'National service framework for children, young people and maternity services' (available from www.dh.gov.uk).

Information Needs and Support

Information and Counselling on Contraception for Women and Girls with FH

- When lipid-modifying drug therapy is first considered for women and girls, the risks for future pregnancy and the fetus while taking lipid-modifying drug therapy should be discussed. This discussion should be revisited at least annually.

Ongoing Assessment and Monitoring

Review

- All people with FH should be offered a regular structured review that is carried out at least annually.

Implementation Tools

Audit Criteria/Indicators

Clinical Algorithm

Patient Resources

Quick Reference Guides/Physician Guides

Resources

Slide Presentation

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Collaborating Centre for Primary Care. Identification and management of familial hypercholesterolaemia. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 Aug. 45 p. (Clinical guideline; no. 71).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2008 Aug (reaffirmed 2011)

Guideline Developer(s)

National Collaborating Centre for Primary Care - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Clinical Excellence (NICE)

Guideline Committee

Guideline Development Group

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

At each Guideline Development Group (GDG) meeting, all GDG members declared any potential conflict of interests (See the "Full guideline appendix G: Declaration of Interests" in the "Availability of Companion Documents" field.)

Guideline Status

This is the current release of the guideline.

The National Clinical Guidelines Centre (formerly the National Collaborating Centre for Primary Care) reaffirmed the currency of this guideline in 2011.

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) format from the National Institute for Health and Clinical Excellence (NICE) Web site .

Availability of Companion Documents

The following are available:

- Identification and management of familial hypercholesterolaemia (FH). Full guideline. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 Aug. 244 p. (Clinical guideline; no. 71). Electronic copies: Available in Portable Document Format (PDF) format from the National Institute for Health and Clinical Excellence (NICE) Web site .
- Familial hypercholesterolaemia: guidelines scope. Full guideline appendix A. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 Aug. 10 p. (Clinical guideline; no. 71). Electronic copies: Available in Portable Document Format (PDF) format from the NICE Web site .
- Familial hypercholesterolaemia: key clinical questions and searches. Full guideline appendix B. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 Aug. 50 p. (Clinical guideline; no. 71). Electronic copies: Available in Portable Document Format (PDF) format from the NICE Web site .
- Familial hypercholesterolaemia: clinical data extractions and excluded studies. Full guideline appendix C. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 Aug. 170 p. (Clinical guideline; no. 71). Electronic copies: Available in Portable Document Format (PDF) format from the NICE Web site .
- Familial hypercholesterolaemia: health economic extractions and excluded studies. Full guideline appendix D. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 Aug. 8 p. (Clinical guideline; no. 71). Electronic copies: Available in Portable Document Format (PDF) format from the NICE Web site .
- Familial hypercholesterolaemia: health economic modelling. Full guideline appendix E. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 Aug. 56 p. (Clinical guideline; no. 71). Electronic copies: Available in Portable Document Format (PDF) format from the NICE Web site .
- Familial hypercholesterolaemia: Simon Broome diagnostic criteria for index individuals and relatives. Full guideline appendix F. London

(UK): National Institute for Health and Clinical Excellence (NICE); 2008 Aug. 6 p. (Clinical guideline; no. 71). Electronic copies: Available in Portable Document Format (PDF) format from the NICE Web site.

- Familial hypercholesterolaemia: Declaration of interests. Full guideline appendix G. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 Aug. 7 p. (Clinical guideline; no. 71). Electronic copies: Available in Portable Document Format (PDF) format from the NICE Web site.
- Familial hypercholesterolaemia. Identification and management of familial hypercholesterolaemia. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence; 2008 Aug. 19 p. (Clinical guideline; no. 71). Electronic copies: Available in Portable Document Format (PDF) from the NICE Web site.
- Familial hypercholesterolaemia. Costing report. Implementing NICE guidance. London (UK): National Institute for Health and Clinical Excellence; 2009 Dec. 42 p. (Clinical guideline; no. 71). Electronic copies: Available in Portable Document Format (PDF) from the NICE Web site.
- Familial hypercholesterolaemia. Costing template. Implementing NICE guidance. London (UK): National Institute for Health and Clinical Excellence; 2009. Various p. (Clinical guideline; no. 71). Electronic copies: Available from the NICE Web site.
- Familial hypercholesterolaemia. Implementing NICE guidance. Slide set. London (UK): National Institute for Health and Clinical Excellence; 2008. 13 p. (Clinical guideline; no. 71). Electronic copies: Available from the NICE Web site.
- Familial hypercholesterolaemia. Audit support. London (UK): National Institute for Health and Clinical Excellence; 2008. 11 p. (Clinical guideline; no. 71). Electronic copies: Available in Portable Document Format (PDF) from the NICE Web site.
- The guidelines manual 2006. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 April. Electronic copies: Available in Portable Document Format (PDF) from the NICE Archive Web site.

Patient Resources

The following is available:

- Inherited high cholesterol in the family (familial hypercholesterolaemia). Understanding NICE guidance - Information for people who use NHS services. London (UK): National Institute for Health and Clinical Excellence; 2008 Aug. 8 p. (Clinical guideline; no. 71). Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This summary was completed by ECRI Institute on February 24, 2010. This summary was updated by ECRI Institute on June 27, 2011 following the U.S. Food and Drug Administration advisory on Zocor (simvastatin). This summary was updated by ECRI Institute on July 15, 2011 following the U.S. Food and Drug Administration advisory on Chantix (varenicline). This summary was updated by ECRI Institute on April 13, 2012 following the U.S. Food and Drug Administration advisories on Statin Drugs and Statins and HIV or Hepatitis C drugs. This summary was updated by ECRI Institute on January 14, 2013 following the revised U.S. Food and Drug Administration advisory on Chantix (varenicline). The currency of the guideline was reaffirmed by the developer in 2011 and this summary was updated by ECRI Institute on October 30, 2013. This summary was updated by ECRI Institute on March 7, 2014 following the U.S. Food and Drug Administration advisory on Low Molecular Weight Heparins. This summary was updated by ECRI Institute on April 8, 2015 following the U.S. Food and Drug Administration advisory on Chantix (varenicline).

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